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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,518	05/01/2002	Audrey Goddard	10466/303	8147

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,518	GODDARD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 September 2005 has been entered.

2. Claims 1-3 are canceled.

Claims 4-6, 9-10 and 14-15 have been amended.

3. Claims 4-17 are pending and under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Rejections Withdrawn

6. The rejection of claims 4-6, 9-10, 12 and 14-17 under 35 U.S.C. 112, second paragraph as being indefinite is withdrawn in view of the amendments to the claims.

Specification

7. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, i.e., "PRO1864 Polypeptides".

Response to Arguments/NEW GROUNDS of REJECTIONS

8. The rejection of claims 4-17 under 35 U.S.C 101 because the claimed invention is not supported by a substantial asserted utility or a well-established utility is maintained and made again.

The response filed 9/30/2005 has been carefully considered, but is deemed not to be persuasive. Applicant reviews the evidentiary standard regarding the legal presumption of utility. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Applicant argues that the utility need not be proved to a statistical certainty, a reasonable correlation between the evidence and the asserted utility is sufficient and applicant cites numerous case law in support of applicants arguments that for a therapeutic and diagnostic use, utility does not have to be established to an absolute certainty and the evidence need not be direct evidence so long as there is a reasonable correlation between the evidence and the asserted utility. Applicant argues that as set forth in MPEP 2107 II(B)(1) "If applicant has asserted that the claimed invention is useful for any particular practical purpose... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." In response to these arguments, the examiner agrees with Applicant's statement that absolute certainty is not the legal standard for utility. However, the rejection does not question the presumption of truth, or credibility, of the asserted utility. The asserted utilities of cancer diagnostics and cancer therapeutics for the claimed polypeptides are credible and specific, however, they are not substantial. The data set forth in the specification are preliminary at best

because the specification does not teach the expression of the PRO1864 polypeptide nor any particular biological activity of the polypeptide. Applicant summarizes their arguments and the disputed issues involved (page 12 of Applicant's response). Applicant reiterates that Example 18 in the specification shows that mRNA encoding the PRO1864 polypeptide is more highly expressed in melanoma compared to normal skin tissue and applicant asserts that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein and based on the identification of the mRNA encoding the PRO1864 polypeptide being more highly expressed in melanoma compared to normal skin applicant asserts that the PRO1864 polypeptide is useful as a diagnostic tool for the determination of the presence or absence of tumor. In support, applicant again argues with the declaration of J. Christopher Grimaldi (previously submitted 5/2/2005) that there is at least a two-fold difference in PRO1864 mRNA between melanoma and normal skin tissue. This has been fully considered, but is not found persuasive. First, it is important to note that the instant specification provides no information regarding PRO1864 polypeptide levels in tumor samples relative to normal samples nor is there any information as to the significance of the expression. Only gene expression data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 4-17 based upon 35 U.S.C. 101 and 112, first paragraph, since it is limited to a discussion of data regarding the gene expression of the PRO1864 cDNA and not gene expression levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. There is no

evidentiary support to Dr. Grimaldi's statement that if a difference in gene expression is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor. Further, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Applicant criticizes Hu et al (2003, Journal of proteome Research 2:405-412, cited on PTO-892 mailed 1/31/2005) for being based upon a statistical analysis of information from published literature rather than from experimental data. Applicant characterizes Hu et al as being limited to estrogen-receptor-positive breast tumor only. Appellant criticizes the types of statistical tests performed by Hu. Applicant concludes that, based on the nature of the statistical analysis performed in Hu, and the fact that Hu only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on the presumption that increased mRNA production leads to increased protein production. Hu is directly on point by showing that this presumption is incorrect when designating protein as diagnostic markers for cancer. Hu analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or

more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21(9):976-977). The instant specification does not disclose that PRO1864 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu, the skilled artisan would not reasonably expect that PRO1864 protein can be used as a cancer diagnostic. Additionally, Hanna J. S. et al (Pathology Associates Medical Laboratories, 1999, Ids reference 19 filed 5/2/2005) show that gene amplification does not reliably correlate with polypeptide over-expression, and thus, the level of polypeptide expression must be tested empirically. The instant specification does not provide additional information regarding whether or not PRO1864 polypeptide is overexpressed in melanomas, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Applicant's criticism of Hu et al's statistical analysis, Applicant is holding Hu et al to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicant's criticism of Hu et al as being limited to a specific type of breast tumor, Hu et al is cited as one of several pieces

of evidence that gene expression in a tumor does not correlate protein expresssion. Considering the evidence of record as a whole, there is no correlation between mRNA levels and protein levels. In view of the totality of the evidence, including the declaration submitted under 37 CFR 1 .132 and the publications of record, the instant utility rejection is appropriate.

Applicant reiterates that they have established that the accepted understanding in the art is that there is a positive correlation between mRNA levels and the level of expression of the encoded protein and applicant argues with the previously submitted second declaration of J. Christopher Grimaldi (previously submitted 5/2/2005), which states that "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed ...the gene product or polypeptide will also be over-expressed.... This same principle applies to gene under-expression." Applicant also argues with the declaration of Dr. Paul Polakis (previously submitted 5/2/2005) which states that based upon his experience accumulated in more than 20 years of research, that it is his scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase of the encoded protein in the tumor cell relative to the normal cell and that based on his experience although reports exist where such a correlation does not exist, such reports are exceptions to a commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Further, the Grimaldi declaration refers to the dogma that a change in mRNA will represent a similar change in protein (item #5 of the Grimaldi declaration labeled as Exhibit 2) and the

Polakis declaration states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. Applicant also cites Alberts [a] (4th ed. 2002; Ids reference 15 filed 5/2/2005), Alberts [b] (3rd ed. 1994; Ids reference 14 filed 5/2/2005), Lewin B. (Genes IV, 1997, Ids reference 21 field 5/2/2005) and Zhigang et al (World Journal of Surgical Oncology, 2:13, 2004, Ids reference 25 filed 5/2/2005) for support that mRNA expression correlates with protein expression. The declarations of Dr. Grimaldi and Dr. Polakis and applicant's arguments have been fully considered, but are not found persuasive. First, the Examiner assumes that the declarations of Dr. Grimaldi and Dr. Polakis are referring to the central dogma of molecular biology as originally formulated by Crick F. and re-stated in the 1970 Nature publication (Nature 227:561-563, 1970). According to Crick, the central dogma only speaks to the flow of information, i.e., the residue-by-residue transfer of sequential information, stating that such information cannot be transferred from protein to either protein or nucleic acid. The Examiner is not aware of any changes to the central dogma of Crick, such as drawing quantitative correlations between levels of mRNA and protein and the declarations do not provide any objective evidence such that the examiner can independently draw conclusions. Further, it is important to note that Alberts [b] and Lewin actually support the fact that further research would have to be carried out to determine if the polypeptide expression levels track with the expression levels of the corresponding mRNA. Alberts [b] and Lewin show that there are several levels that control gene expression both at the transcriptional (i.e., mRNA synthesis) and the translational (i.e., protein production)

levels. It is also important to note that transcription occurs in the nucleus, whereas translation occurs in the cytoplasm (see Fig. 9-2, page 403 of Alberts[b]). Thus, one skilled in the art would not accept that increased mRNA levels directly correlate with the level of the corresponding polypeptide in view of the multitude of controls at the transcriptional and translational levels. With respect to applicant's arguments regarding the art of Zhigang et al, the examiner agrees that statistical certainty is not the standard to establish an asserted utility, however, the experiments of Zhingang evince that one needs to actually determine the expression of the protein to be sure of expression. Applicant also argues that Alberts [a] (4th ed. 2002, Ids reference 15 filed 5/2/2005). figure 6-3 on page 302 illustrates the general principle that there is a correlation between increased gene expression and increased protein expression. In response to this argument, while increased transcript levels can lead to increased polypeptide levels, there are other regulatory factors that also effect the rate of translation as evidenced by Alberts [b] as shown in Figure 9-72. Additionally, Meric et al (Molecular Cancer Therapeutics, 1:971-979, 2002, Ids reference 23 filed 5/2/2005) teaches that in addition to variations in mRNA sequences that increase or decrease translational efficiency, changes in the expression or availability of components of the translational machinery (i.e., over-expression of eIF4E, eIF4G, eIF-2α, eIF-4A1, ect...) as well as activation of translation through aberrantly activated signal transduction pathways also effect the rate of translation in cancerous cells. The instant application only analyzes PRO 1864 mRNA expression and Figure 6-3 of Alberts [a] (4^{th} ed. 2002) does not account for these other types of controls in cancerous cells. Further, Meric et al in

agreement with Alberts [b] and Lewin acknowledges that gene expression is quite complicated and is regulated at the level of mRNA stability, mRNA translation and protein stability and Meric goes on to discuss that the components of the translation machinery and signal pathways involved in the activation of translation initiation represent good targets for cancer therapy (see pages 975-976). If it is the accepted understanding in the art that there is a direct correlation between mRNA levels and the level of expression of the encoded polypeptide, there would not be a need to target the translational machinery, unless of course the two are separate.

Applicant argues the art of Gokman-Polar and Gygi, stating that there was a general trend of increased protein levels resulting from increased mRNA levels and applicant criticizes Gygi stating that Gygi has nothing to do with changes in protein levels resulting from changes in mRNA levels and does not support the Examiner's position. Again, Gokman-Polar indicate that mRNA levels do not necessarily correlate with protein levels and evince that expression may be regulated at the posttranscriptional/translational level. With respect to Gygi, it is reiterated that Gygi et al found that even similar mRNA expression levels could be accompanied by a wide range (up to 20-fold difference) of protein abundance levels, and vice versa. Applicant criticizes Gygi, stating Gygi has nothing to do with changes in protein levels resulting from changes in mRNA levels and does not support the Examiner's position. With respect to Applicant's criticism of Gygi, Applicant is holding Gygi to a higher standard than their own specification, which provides no evidence or correlation between increased PRO1864 mRNA levels and increased PRO1864 protein levels. Further, it is

important to note that it is applicant's position that increased mRNA leads to an increase in protein levels. Gygi actually support's the Examiner's position which states that there is no necessary correlation between mRNA levels and protein levels and one cannot predict protein levels from mRNA. The instant specification does not provide information regarding whether or not the PRO1864 protein is overexpressed in melanomas compared to normal skin. In agreement and citing Gygi, Greenbaum et al (Genome Biology, 2003, Vol. 4, Issue 9, pages 117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship

between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood.

Also, Haynes et al (1998, Electrophoresis 19:1862-1871, PTO-892 mailed 1/31/2005), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and mRNA levels. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes et al concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). In agreement with Gygi and Haynes, Lian et al (Blood 98:513-524, 2001) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al (The Journal of Biological Chemistry 277:31291-31302, 2002) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (page 31291, abstract). Even more recently, Hanash S. [a] (Nature Reviews, Applied Proteomics Collection, pp. 9-14, March 2005,. Ids reference 10 filed 9/30/2005) states "There is a need to profile gene expression at the level of the proteome and to correlate changes in gene-expression profiles with changes in proteomic profiles. The two are not always linked-numerous alterations occur in protein levels that are not reflected at the RNA level." (see page 12). Further, Hanash [a] teaches that tumors are complex biological systems and no single type of molecular

approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics (see abstract). Hanash et al [b] (The Pharmacogenomics Journal, 3(6):308-311, 2003, Ids reference 9 filed 9/30/2005) states "However perfected DNA microarrays and their analytical tools become for disease profiling, they will not eliminate a pressing need for other types of profiling technologies that go beyond measuring RNA levels, particularly for disease-related investigations." (see page 311). According to Hanash et al [b], there is a need to assay protein levels and activities and numerous alterations may occur in proteins that are not reflected in changes at the RNA level (see page 311). Clearly, contrary to applicant's arguments and as evidenced by the art above, it is not well-established, nor the standard in the art that there is a direct correlation between mRNA levels and the level of expression of the encoded protein. The literature supports that RNA expression cannot inevitably be correlated with levels of the encoded polypeptide and one skilled in the art would not presume that the levels of RNA are necessarily predictive of the levels of the encoded polypeptide given the distinct regulation of transcription and translation as evidenced by Hu et al, LaBaer, Hanna et al, Alberts[a], Alberts[b], Lewin, Zhigang et al, Meric et al, Gokman-Polar, Gygi et al, Greenbaum et al, Haynes et al, Lian et al, Fessler et al, Hanash S [a] and Hanash et al [b]. One skilled in the art would do further research to determine whether or not the PRO1864 protein was overexpressed in melanomas compared to normal skin tissue. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This

further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. M.P.E.P 2107 I states:

> A '"substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In view of the totality of the evidence, the rejection for lack of utility is proper and is maintained.

9. The rejection of claims 4-17 under 35 U.S.C. 112, first paragraph, is maintained. Specifically, since the claimed invention is not supported by a substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. The rejection of claims 4-5, 12-17 under 35 U.S.C 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention is maintained.

The response filed 9/30/2005 has been carefully considered, but is deemed not to be persuasive. Applicant reviews the evidentiary standard regarding the legal presumption of written description. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of written description. The response argues that the claims have been amended to recite that the

claimed polypeptides have at least 95% amino acid sequence identity to several polypeptides related to SEQ ID NO:14 and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in melaonoma compared to normal skin tissue respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in melaonoma compared to normal skin tissue" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:14 in skin tissue samples." Applicant argues that the instant claims are analogous to the claims discussed in Example 14 of the written description training materials, in which written description was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular activity, even though applicant had not made any variants. Unlike example 14, which encompasses a genus of molecules having significant structural similarity and identical biological functions, the nucleic acids of the present claims may have functions and structures that differ greatly from that of PRO1864, therefore, one of skill in the art would not be able to identify the encompassed molecules as being identical to those instantly claimed. Further, the specification does not disclose any polypeptide that is 95% or 99% identical to SEQ ID NO:14 and more highly expressed in melaonoma compared to normal skin tissue. Conception does not occur unless one has a mental picture of the structure of the molecule, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.

Additionally, the claims encompass polypeptides where the only distinguishing characteristic is partial structural identity with SEQ ID NO:14, such as 95% or 99% amino acid sequence identity with amino acids 21-53, 119-129 or 167-234 of SEQ ID NO:14. There is no functional limitation with respect to these partial structures of SEQ ID NO:14 and as above, the encompassed polypeptides may have substantially different structures and biological functions. This is not similar to example 14 of the written description training materials, which is drawn to polypeptides having 95% homology to a particular full-length sequence and possessing a particular catalytic activity, which uniquely distinguishes members of the genus by structure and function. The only distinguishing characteristic of the present claims is sequence identity or partial sequence identity.

Applicant remarks the PTO has issued many patents containing claims to variant sequences where applicants did not actually make such nucleic acids or proteins. In response to this argument, applicant is reminded that each patent application is examined on its own merits and the examiner does not know the prosecution history of these cases and will not comment on the prosecution history.

11. The rejection of claims 4-17 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 9/30/2005 has been carefully considered, but is deemed not to be persuasive. The response argues as above for the utility rejection that in general differential expression levels of mRNA leads to differential protein expression levels and the references cited by the examiner are exceptions to the general rule. In response to this argument, the examiner's arguments above apply here as well and the art of record discussed above underscores the unpredictability in the art and the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. The response also states that Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression and thus, is not relevant. The examiner agrees with applicant's assessment of Pennica et al.

With respect to the protein variants encompassed by the claims, applicant argues that in view of the homology levels recited in the claims and functional limitations relating to differential expression or the ability to generate an antibody which can be used to detect the polypeptide of SEQ ID NO:14 in skin samples, there is not substantial variation within the species encompassed by the claims. Again, Applicant has not provided sufficient guidance to assist one skilled in the art to make and use the claimed protein variants that are 95% or 99% identical to SEQ ID NO:14 much less variants that are 95% or 99% identical to amino acids 21-53, 119-129 or 167-234 of SEQ ID NO:14 in a manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments. The specification does

not teach a biological function of the claimed polypeptides and one of skill in the art would not know how to use the claimed polypeptides or screen for the same. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Due to the large quantity of experimentation necessary to generate the indefinite number of protein variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art (Burgess et al, Lazar et al, Schwartz et al, Lin et al and Li et al, previously cited in the Office Action mailed 1/31/2005) which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant reiterates that there is not substantial variation within the sequences of the polypeptides encompassed by the claims and applicant maintains that the claims do not encompass an unreasonable number of inoperative species. In response to this

argument, it is respectfully pointed out that the claims are drawn to polypeptides having at least 95% identity with portions of the polypeptide of SEQ ID NO:14, i.e., amino acids 21-53, 119-129 or 167-234 and wherein said portions may be fused to amino acids 1-20 of SEQ ID NO:14 (i.e., the signal peptide). Thus, the claims encompass polypeptides having substantial variability to the polypeptide of SEQ ID NO:14. The specification does not teach any function or biological activity of the claimed portions and one skilled in the art would be forced into undue experimentation to determine how to use such variants.

Applicant remarks the PTO has issued many patents containing claims to variant sequences where applicants did not actually make such nucleic acids or proteins. In response to this argument, applicant is reminded that each patent application is examined on its own merits and the examiner does not know the prosecution history of these cases and will not comment on the prosecution history.

The Examiner acknowledges Applicant's remarks at page 27 of the response, however, Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

12. Claims 4-6, 10 and 12-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the

claimed invention at the time the application was filed is maintained. This is a NEW MATTER rejection.

The response filed 9/30/2005 has introduced NEW MATTER into the claims. As presently amended, the claims recite polypeptides having at least 95% amino acid sequence identity to polypeptides comprising the signal peptide of SEQ ID NO:14 (i.e., amino acids 1-20 of SEQ ID NO:14) fused to a portion of SEQ ID NO:145 selected from amino acids 21-53, 119-129 and 167-234 and chimeric polypeptides thereof further comprising a heterologous polypeptide. The response did not point out where support for these newly presented limitations could be found in the originally filed disclosure. The specification does provide adequate written support for polypeptides comprising amino acids 1-20 of SEQ ID NO:14 fused to the recited portions of SEQ ID NO:14 and polypeptides having at least 95% amino acid identity to said polypeptides. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant should therefore specifically point out the support for any amendments made to the disclosure."). As presently amended, the claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the presently amended claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to

provide sufficient written support for the limitations recited in the present claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

Conclusions

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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SUPERVISORY PATENT EXAMINER